REMARKS

An interview summary statement accompanies this amendment.

35 U.S.C. § 103(a)

The Office rejected claims 119-146 as allegedly obvious in view of U.S. patent No. 5,461,042 (hereafter the '042 patent) or U.S. patent No. 5,387,583 (hereafter the '583 patent) in view of D.J.J. Carr, *J. Neuroimmunol.*, 89:160-167, 1998 (hereafter 'Carr'). Applicants respectfully request reconsideration in view of the amended claims and the comments below.

The record includes evidence of unexpected efficacy in eliciting an increase in neutrophils in humans and non-human primates as shown by the declaration Applicants submitted on February 21, 2007 at paragraphs 7, 8, 14 and 18. Those results could not have been predicted from the cited references, which are all silent about neutrophil responses in humans. This is evidence of record that the subject matter the amended claims recite was not obvious in view of the cited references. The February 21, 2007 declaration also shows evidence of increased survival in lethally irradiated non-human primates using 3β,17β-dihydroxyandrost-5-ene as a monotherapy, which was an unexpected and unpredictable result (paragraphs 13 and 14). Applicants respectfully request reconsideration of that evidence in view of the amended claims and the cited references. Applicants believe that these results suffice to rebut *prima facie* obviousness under 35 USC § 103 to the extent that such exists in view of the cited references. Evidence of unexpected results can rebut *prima facie* obviousness under 35 USC § 103(a). *Graham v. John Deere Co. of Kansas City*, 86 S.Ct. 684, 148 U.S.P.Q. 459 (1966).

The amended claims recite a specific drug treatment regimen (5 consecutive daily doses of 3β,17β-dihydroxyandrost-5-ene), intramuscular administration and specific dosages in a dose range (200 - 300 mg) that resulted in increased neutrophil numbers in humans in phase 1 safety studies. The cited references do not disclose either the recited treatment regimen or any unit doses in the 200 - 300 mg range.

Evidence of the neutrophil response in humans is of record in the February 21, 2007 declaration at paragraph 7, 8 and 18. The recited dosages of the amended claims, 200 - 300 mg/day, are well above the maximum daily 30 mg oral dose of 3β,17β-dihydroxyandrost-5-ene that the '042 patent discloses for "larger adult animals" at column 17, lines 38-47, with lower doses indicated for routes of administration such as subcutaneous administration. The '583 patent discloses at column 19, line 65 through column 20, line 2 daily 15 or 30 mg oral unit doses combined with 5 or 10 mg of dexamethasone. The *in vivo* data in the '042 patent was obtained using mice. The '583 patent discloses no specific dosages for intramuscular administration and Carr describes subcutaneous administration of 32, 100 or 320 mg/kg of 3β,17β-dihydroxyandrost-5-ene with no mention of any neutrophil response in humans or mice.

The Carr reference describes treatment of a viral infection (HSV-1) in mice using 3β,17β-dihydroxyandrost-5-ene, which is a different clinical indication. Carr described the capacity of 3β,17β-dihydroxyandrost-5-ene to increase NK cell activity in mice but it did not increase NK cell numbers (see Carr at section 3.4 at page 164). NK cells are lymphocytes, not neutrophils. Carr makes no suggestion about what activity, if any, the compound would have in humans to increase neutrophils. Applicants respectfully submit that Carr, when combined with the '042 and/or '583 patents does not suggest any protocol or dosage that would necessarily result in a neutrophil increase in humans.

At page 3, the Office asserted that "the determination of a treatment regimen is routine in the medical art". Applicants believe this assertion implied that the treatment regimen was thus an aspect of the claimed subject matter that could not be part of a claimed method because the subject matter of the claim as a whole was obvious in view of the references. The threshold issue remains of whether or not the claimed subject matter was obvious in view of the references. The Supreme Court stated: "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the

product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Intl. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). Applicants note that the *KSR v. Teleflex* decision came from the mechanical arts, not the medical arts. In that case, the court stopped short of creating a rigid *per se* rule of obviousness by stating that if a solution to a problem was obvious to try, then that *might* show that it was obvious under 35 USC § 103. In stating that when "there is a design need or market pressure to solve a problem", the KSR court recognized that in establishing obviousness under 35 USC § 103, there needs to be at least some motivation to arrive at claimed subject matter. Absent that motivation, essentially everything would be *prima facie* obvious.

In the present case, the cited references did not reveal any "design need or market pressure to solve a problem", because the cited references did not reveal to one of ordinary skill in the art anything about the capacity of 3β,17β-dihydroxyandrost-5-ene to elicit a neutrophil response in humans. Carr suggests that the compound increased NK cell activity in mice with HSV-1 infections, but that does not relate to any type of neutrophil response in humans. Given that, what problem in treatment of humans was there for one of ordinary skill in the art to solve? The court has stated "a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103" *In re Sponnoble* 405 F.2d 578, 585 (C.C.P.A. 1969). See also, *Cross Medical Products, Inc. v. Medtronic Sofamor Danek, Inc.* 424 F.3d 1293, 76 U.S.P.Q.2d 1662 (Fed. Cir. 2005). Similarly, for the claimed subject matter there was no "finite number of identified predictable solutions" the *KSR v. Teleflex* court referred to because there was no way that one of ordinary skill in the art could know with reasonable predictability from Carr and the '042 and '583 patents that 3β,17β-dihydroxyandrost-5-ene would elicit a neutrophil increase in humans.

The *KSR v. Teleflex* Supreme Court decision did not hold that any portion of 35 USC § 103 was unconstitutional and thus that statute remains in effect. Section 103 states in part: “Patentability shall not be negatived by the manner in which the invention was made.” In interpreting this language, the court has stated that “patent acquisition does not require any threshold level of effort or ingenuity. See 35 U.S.C. § 103(a) (2000) ("Patentability shall not be negatived by the manner in which the invention was made."); 35 U.S.C. § 103 Revision Notes and Legislative Reports, 1952 Notes ("It is immaterial whether [the invention] resulted from long toil and experimentation or from a flash of genius."); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) (stating that "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute").” *CFMT, Inc v. Yieldup International Corp.*, 349 F.3d 1333, 1340; 68 U.S.P.Q.2D 1940 (Fed. Cir. 2003).

Applicants respectfully submit that whether or not a portion of a claim was determined by routine experimentation is not dispositive of obviousness under 35 USC § 103. The issue is whether or not the cited references collectively make obvious what is now claimed, not whether or not a claim limitation was attained by routine experimentation. The Supreme Court in *KSR v. Teleflex* understood this and stated: “When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as Adams, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of

necessity will be combinations of what, in some sense, is already known." *KSR v. Teleflex* 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Supreme Court was again commenting on the mechanical arts in referring to "the combination of two known devices according to their established functions". In the present case, the function of 3β,17β-dihydroxyandrost-5-ene was not known. The cited references lead to no identified "design need or market pressure" that would lead one of ordinary skill in the art to contemplate the subject matter of the amended claims.

At page 3 of the office action the Office asserted that the "discovery that said enhancement is due to an increase in the number or activity of neutrophils in circulation in the human does not lend patentability to the claimed process because said is inherent to the compound". Applicants respectfully traverse this statement. As noted above, the discovery of a problem can lead to patentability, even if the solution to the problem were obvious. *In re Sponnoble* 405 F.2d 578, 585 (C.C.P.A. 1969). When considering the relationship of inherency and obviousness, the court has stated: "Inherency and obviousness are distinct concepts. *W. L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1555; 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983) (citing *In re Spormann*, 363 F.2d 444, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966)), cert. denied, 469 U.S. 852, 105 S. Ct. 172, 83 L. Ed. 2d 107 (1984)." *Kloster Speedsteel AB, v. Crucible Inc.*, 793 F2d 1565, 230 USPQ 81 (Fed. Cir. 1986). The court has also stated: "As we pointed out in *In re Adams*, 53 CCPA 996, 356 F.2d 998, 148 USPQ 742 [(1966)], the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753 (C.C.P.A. 1977). Applicants respectfully submit that the neutrophil response seen in humans is not "inherent to the compound" as asserted in the office action at page 3. The maximum daily 30 mg dosage the '042 patent expressly teaches would not significantly increase neutrophils in humans as shown by Applicants' data in the February 21, 2007 declaration at paragraph 7, where 5 consecutive 200 mg daily doses were needed to attain neutrophil increases in humans.

At page 3 of the office action, 3rd full paragraph, the Office asserted that the claimed invention "is drawn to the use of androstenediol to treat or ameliorate immune suppression in human." Applicants respectfully traverse this characterization as overbroad. The amended claims treatment of innate immune suppression that is associated with recited radiation exposure. Innate immune suppression does not always occur in the various clinical conditions the cited references describe. For example, Carr described treatment of acute HSV-1 infection, not any innate immune suppression condition. Applicants are thus not claiming subject matter as broadly as the Office asserts.

Applicants respectfully submit that the claimed subject matter is not *prima facie* obvious in view of the unexpected results described in the February 21, 2007 declaration and in view of the cited references alone. Applicants respectfully request reconsideration and allowance of the amended claims.

Concluding remarks

Please charge any additional fees, except the issue fee, that are due now (except the issue fee), or credit any overpayment to Deposit Account No. 501536. The undersigned invites the Examiner to call the undersigned to clarify any matters or questions that may occur to the Examiner.

Respectfully submitted,

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